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Research paper

A computational investigation of cytosine and 5-methyl cytosine reactivity by means of ionization potentials and one specific methylation pathway

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HIGHLIGHTS

- Cytosine and 5-methyl cytosine ionization potentials.
- Methylation activation barriers of cytosine by methane diazonium ion.
- HOMO-LUMO gap and HSAB.
- C-PCM and SM8 solvation models.

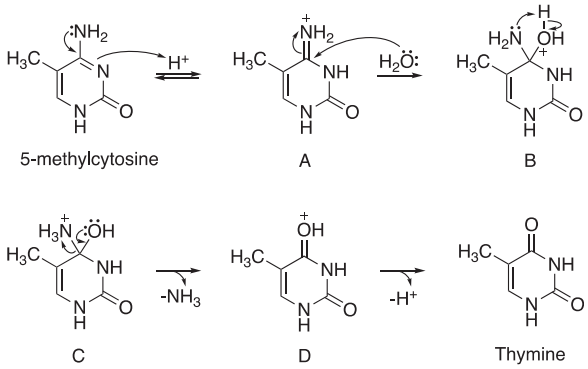
ABSTRACT

Results from DFT/ωB97X-D/6-311 + G**/C-PCM calculations show that the aqueous vertical IP of 5-methylcytosine is lower than that of cytosine by 0.25 eV. Using the HSAB concept, the HOMO-LUMO gap for 5-methylcytosine is smaller than that of cytosine, making it soft and opt to form covalent bonds and more reactive. Carcinogenic methane diazonium ion can methylate cytosine at the N3 site and mutate it via an S_N2 mechanism and the activation energy is approximately 5.05 kcal/mol in water.

1. Introduction

Much of biochemistry and biophysics of DNA is based on the electronic properties of nucleotides and its components. DNA can be damaged by ionizing radiation and methylated by carcinogenic methylating agents. On one hand, ionizing radiation can make cells to activate a DNA damage response pathway to re-program gene expression [1,2] and its results are established to cause significant genetic damage that can induce mutations [3,4]. On the other hand, in living organisms, DNA methylation is a significant threat to normal cell functioning and it leads to mutation and eventually to cancer and cell death [5,6]. It was reported that as the first π ionization potential of the nucleotide base decreases the base reactivity increases and this comparison provides evidence that electronic factors influence DNA methylation patterns [7].

Among the DNA nucleobases, cytosine (Cyt) is the smallest and most alkaline molecule in aqueous solutions and this feature plays an important role in biochemical processes [8]. The most stable (canonical) form of Cyt is an amino-keto structure, although other less common structures exist, such as the imino-enol structure. Its interaction with methyl groups has been the subject of numerous studies as methylated cytosine can be converted into thymine, which may contribute to genetic mutations. 5-methylcytosine (m^5Cyt) is found in genomic DNA and it is involved in gene transcription. It is inherently mutagenic because it is converted directly to thymine, C → T. The unmethylated cytosine is converted to uracil, which is repaired in a more efficient manner. In the *p53* gene, 28% of the point mutations are attributed to the C → T transitions at CpG dinucleotides because of the deamination of m^5Cyt [9]. The mechanism of C → T conversion is shown below.



The rapid deamination of 5-methylcytosine results in thymine and

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ammonia. Under acidic condition 5-methylcytosine can be easily protonated at N3. The resulting iminium ion A is now very electrophilic at C4 and further undergoes nucleophilic attack by water forming an unstable tetrahedral intermediate B. Intramolecular proton transfer converts amino group into a good leaving group, NH_3, that in turn is kicked out by the lone pairs of the oxygen, D. Finally, deprotonation of the oxonium ion leads to the formation of thymine. The conversion of Cyt to Thy was studied in steered molecular dynamic (SMD) simulations and it was reported that the C → T conversion is spontaneous but slow and more favorable in the gas phase [10].

Cytosine methylation is a common form of post-replicative DNA modification seen in both bacteria and eukaryotes [11]. Methylation can either activate or suppress carcinogenesis [12]. The mechanisms of methylation and demethylation in carcinogenesis remain undetermined and there are questions as to whether the methylation changes are a cause or consequence of cellular transformation and clonal expansion [13]. Cytosine methylation contributes to carcinogenesis by four different ways, a) driving C → T transition mutations in CpG dinucleotides, b) by altering patterns of imprinted gene expression, c) by decreasing chromosome stability and d) by inactivating tumor suppressor genes via *de novo* methylation of their promoters [13]. The main difficulty in determining the mechanisms of methylation of tumors is that the analysis of experimental results cannot separate the methylation from other cellular processes. Unfortunately, it is unknown which cells may inactivate tumor suppressor genes via methylation and for the *de novo* methylation of CpG islands, a stochastic and age-encroachment of methylation patters is adopted.

However, cytosine in double- stranded DNA can be methylated by the carcinogenic methane diazonium ion at the N3 and O^2 sites [14]. The methane diazonium ion is considered to be an ultimate carcinogen. It is the reactive intermediate formed from methyl-*N*-nitrosourea (MeNU) which can react at the ring nitrogen and oxygen atoms of Cyt via an S_N2 reaction mechanism. This reactive intermediate is formed via metabolic activation [5]. Anticancer drugs such as temozolomide (TMZ) and decarbazine (DTIC) and several detrimental methylating agents methylate DNA via the formation of methane diazonium ion [15].

The relative methylation of cytosine by the methane diazonium ion at the N3 site is significantly higher than that at the O^2 site [5]. The pathway of methylation at the N3 site in the cell is under investigation. It is reported in an experimental study aiming to explore the mechanism for N3 methylation of cytosine instead of its preferred reaction at C5 by methyltransferase (DNMT3A) wild type and mutants using liquid chromatography linked to tandem mass spectrometry (LC–MS/MS) that it occurs by an inverted binding of the flipped cytosine into the active-site pocket of the DNA methyltransferase [16]. The cytosine methylation by the methane diazonium ion at the N3 site was discussed in the legendary experimental study of Singer and Grunberger using ds DNA from salmon sperm, calf thymus, salmon testes, rat liver and brain, human fibroblasts, and HeLa and V79 cells. [5]. In our investigation we study the energetics of Cyt methylation at the N3 site by methane diazonium ion.

The fact that as the first π ionization potential of the nucleotide base decreases the base reactivity increases [7] motivates us to evaluate the gas- and aqueous-phase VIP and AIP of Cyt and m^5Cyt. The m^5Cyt represents about 1% of the bases in mammalian cells and it is involved in gene transcription. The radiation-induced damage to Cyt and m^5Cyt in cells is very close to that observed when DNA is exposed to either hydroxyl radicals or one-electron oxidants in aerated aqueous solutions [3].

The UV-induced ionization of Cyt in the gas-phase has been investigated previously experimentally, 8.80 eV, employing He(I) photoelectron spectroscopy [17] and theoretically in a series of high-level theoretical studies and the reported values of the VIP of Cyt were in the range of 8.57 eV [18] to 8.73 eV [19] and 8.78 eV [20].

The ionization of nucleic acid components in solution involve systems with complex interactions. In a hybrid method of combining gas-phase photoelectron spectroscopy data with results from self-consistent field and post-self-consistent field molecular orbital calculations with theoretical Gibbs free energies of hydration the aqueous ionization energies of 5′-dCMP$^-$ was evaluated as 5.50 eV [4]. The values of VIP, AIP, VIP_{aq}, and AIP_{aq} of Cyt, the nucleoside and the nucleotide were evaluated using *ab initio* and QM/MM calculations [20–25].The values span from 5.17 eV up to 11.98 eV depending on the conditions.

The main goals of the present theoretical investigation are to calculate the VIP, AIP and VIP_{aq} and AIP_{aq} values of Cyt and m^5Cyt by employing Density Functional Theory (DFT) with more recent functional and bigger basis set. This is necessary in order to address the big span of these values in literature and get more accurate values employing the DFT. The next goal of this investigation is to determine the relative reactivity of Cyt and m^5Cyt utilizing the HSAB concept [26,27]. For the aqueous-phase calculations we employ the C-PCM and the SM8 solvation models. The VIP values are directly related to the reactivity of Cyt towards methylation by DNA alkylating agents [28]. The third goal of this computational study is to calculate the activation barriers of the Cyt methylation by methane diazonium ion at the N3 site employing the dispersion-corrected density functional M06-2X with the 6-311+G** basis in order to get a more accurate value than the one obtained by Ekanayake et al [14]. And the ultimate goal of this study is to gain new knowledge about DNA damage by relating the ionization potential values of Cyt and its methylation to mutation and damage. Fig. 1 shows the molecules under investigation.

2. Methods

All calculations were performed using the Spartan ’18 Parallel Suite [29] for Microsoft Windows 7, Professional 64-bit edition on an Intel Xeon E3-1240 v3 processor utilizing 32 GB of RAM. Standard geometries of Cyt and m^5Cyt were generated using the Molecule Builder of Spartan ’18 and were fully optimized employing the Density Functional Theory using the hybrid ωB97X-D functional that includes empirical corrections for long-range non-bonded interactions with the 6-311+G** basis set [30].. The same calculations were also repeated by using the Density Functional Theory with the B3LYP functional and the 6–31 + G* basis set.

The 6-311+G** basis set is a triple-zeta basis set of d-type polarization functions and a set of diffuse functions on non-hydrogen atoms and a set of p-type polarization functions on all hydrogen atoms. The 6–31 + G* basis set contains polarization *and* diffuse functions on heavy atoms. These polarization functions affect geometry and energetics and the use of both basis sets are appropriate for the present study. The appropriateness is also underlined by the agreement of results with experimental values, when they are available. There are no experimental data available for all calculations in the present investigation but for the gas-phase IP of Cyt are available and we use the experimental value to check the appropriateness of the theory level employed herein.

Gas-phase adiabatic ionization potentials (AIP) correspond to an ionizing excitation from the optimized geometry of the neutral molecule to an optimized geometry of the radical cation and they were

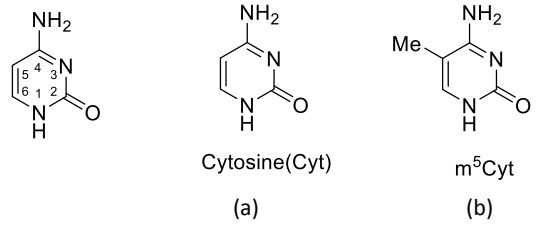


Fig. 1. Structures and atom numbering of cytosine on the left, (**a**) (Cyt), (**b**) 5-methylcytosine (m^5Cyt).

evaluated and reported with zero-point-energy (ZPE) correction, on the average of 0.01 eV. The gas-phase vertical ionization potential (VIP) corresponds to a vertical excitation that occurs at the equilibrium (optimized) geometry of the neutral molecule.

The calculations for the determination of the aqueous ionization potentials (IP_{aq}) were performed employing a) the conductor-like polarizable continuum model (C-PCM) with water being the implicit solvent with dielectric constant of 78.3 [31] and b) the SM8 Universal Solvation Model embedded in the Spartan '18 package. The SM8 Model employs the Generalized Born (GB) approximation for bulk electrostatics and represents the solute molecule as a collection of partial atomic charges in a cavity [31].

The VIP_{aq} is calculated directly by subtracting the total energy of the radical cation from the total energy of the optimized neutral molecule in the condensed phase [32]. Then the hydrated electron stabilization energy, V_o, (-1.6 eV) is added [33,34]. The direct method provides results that are similar to the ones can be obtained via the conventional thermodynamic cycle [33,35]. The non-equilibrated solvent procedure is found to be more accurate for VIE calculations [36].

The principle of hard and soft acids and bases is utilized to determine the relative reactivity of Cyt and m^5Cyt. The interactions between acids and bases are controlled by the relative energies of the participating frontier molecular orbitals (FMO) i.e., HOMO and LUMO, per the relation [26,37]

$$\text{hardness} = (\text{Ionization Energy} - \text{Electron Affinity})/2 = (E_{LUMO} - E_{HOMO})/2 \quad (1)$$

And the greater the energy gap between the HOMO and LUMO, the harder is the species.

The S_N2 transition states of the methylation reaction of Cyt by methane diazonium ion at the N3 site was monitored by the Energy Profile module in Spartan '18, employing the dispersion-corrected density functional M06-2X with the 6-311+G** basis set. We considered using a dispersion-corrected density functional (M06-2X) for better energetics [38]. The optimized structures were confirmed to be true transition states by calculating the normal modes and finding one and only one imaginary frequency. The negative frequency implies a negative force constant which in turn corresponds to one direction in the nuclear configuration space at which the energy is at a maximum value, while in all other orthogonal directions the energy is at a minimum value.

3. Results and discussion

3.1. Ionization potentials of Cyt and m^5Cyt

Table 1 lists results for the gas-phase adiabatic and vertical gas-phase IPs for free base cytosine and 5-methyl cytosine. The adiabatic IPs were corrected for zero-point-energy. The geometry of both molecules was optimized by the DFT/ωB97X-D/ 6-311+G** level of theory. Here the calculated gas-phase VIP for cytosine is 8.84 eV. In a previous theoretical investigation the gas-phase VIP of cytosine was reported as 8.46 eV for the planar geometry and 8,56 eV for the non-planar geometry employing the outer-valence Green's function method (OVGF) [39]. In an earlier experimental investigation employing He(I) photoelectron spectroscopy the gas-phase IP of cytosine was reported to be 8.80 eV [17]. In this experimental study it is pointed out that the photoelectric spectra of cytosine and its derivatives have low resolution (they are rather broad) and this is attributed likely to the presence of several isomers in the sample and to higher probe temperatures required that could give rise to partial decomposition. The calculated value of 8.84 eV for Cyt VIP as listed in Table 1 is greater than the experimental value of 8.80 eV [17] by 0.04 eV. The theoretical gas-phase VIP value of 8.78 eV [20] is closer to the experimental value of 8.80 eV.

Table 1
Gas-phase and aqueous adiabatic and vertical ionization potentials for Cyt and m^5Cyt calculated at the DFT/ωB97X-D/6-311+G** level of theory and the C-PCM reaction field model. The adiabatic ionization potentials were corrected for the zero-point-energy, (ZPE). $V_o = -1.6$ eV.

Molecule	$AIP_{(gas)}$ (eV)	$VIP_{(gas)}$ (eV)	$AIP_{(aq)} + V_o$ (eV)	$VIP_{(aq)} + V_o$ (eV)
Cyt	8.75	8.84	4.90	5.11
m^5Cyt	8.41	8.52	4.63	4.86
m^1Cyt	8.45			

The gas-phase AIP for Cyt as listed in Table 1 is 8.75 eV. Unfortunately, there is no experimental data to compare the theoretically obtained values for the gas phase AIP of Cyt. The experimental value of gas-phase AIP of 1-methylcytosine (m^1Cyt) (8.19 eV) was used to evaluate the aqueous threshold ionization potential of 5-$dCMP^-$ (5.50 eV) [4]. Calculating the gas-phase AIP of m^1Cyt using our methodology and the DFT/ωB97X-D/ 6-311+G** level of theory we get the value of 8.45 eV, which is 0.14 eV higher than the experimental value.

The same calculations were repeated employing the DFT/B3LYP/6–31 + G* level of theory in order to check the results of our calculations and establish an uncertainty in our values and the data is listed in Table A in Supporting Information. According to the results of these calculations the VIP of Cyt is 8.69 eV and the AIP is 8.56 eV and for the m^1Cyt the AIP value is 8.33 eV. The value for the VIP of Cyt is 8.69 eV, as calculated at the DFT/B3LYP/6–31 + G* level of theory and it is closer to other theoretically obtained values [18,39,40] for the same property. The values obtained with the DFT/B3LYP/6–31 + G* level of theory are lower than the ones obtained by the level listed in Table 1 by 0.19 and 0.15 eV for the AIP and VIP of Cyt and by 0.12 eV for both properties of m^1Cyt. At this point we should point out that the functional ωB97X-D contains dispersion terms and the basis set 6-311+G** is larger than the 6–31 + G* for better energetics studies.

The AIP_{aq} and VIP_{aq} of Cyt in water are calculated by the DFT/ωB97X-D/ 6-311+G**/CPCM level of theory and they are 4.90 eV and 5.11 eV respectively. These VIP_{aq} values are listed in Table 1, and they are in agreement with the values reported in previous investigations providing that the stabilization energy of the hydrated electron is taken as −1.6 eV instead of −1.3 eV, as it was estimated in previous years [4,39].

The AIP_{aq} and VIP_{aq} of Cyt values, using DFT/B3LYP/6–31 + G /SM8 level of theory are listed in Table A in Supporting Information and they are 4.97 eV and 5.08 eV, respectively. In in fact they closer to the ones listed in Table 1.

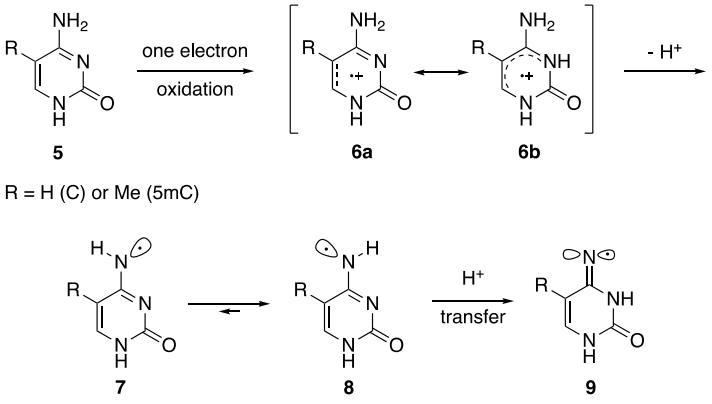
The issue of microhydration to bulk hydration was addressed by previously reported data on thymine [25] and guanine [41]. In the guanine investigation local ionization maps show clearly that microhydration leads to the formation of donor and acceptor H-bonds in a similar manner as in the case for thymine. However, at bulk hydration, where all the H-bonds are averaged over a large number of water molecules this H-bond effect is eliminated, a conclusion consistent with the report of the effect of microhydration on the ionization energy of thymine [42]. In light of these previous investigations on microhydration of thymine and guanine, here the reported values for the aqueous ionization potential values of Cyt are well estimated.

The gas-phase AIP and VIP of m^5Cyt listed in Table 1 are 8.41 eV and 8.52 eV respectively. The experimental value of VIP for m^5Cyt is 8.78 eV [17]. The calculated values for m^5Cyt are ~ 0.32 eV lower than that of Cyt and in water the AIP_{aq} is 4.63 eV and the VIP_{aq} is 4.86 eV, lower by ~ 0.25 eV than that of Cyt. The hard and soft acids and bases theory predicts that a molecule with a smaller HOMO – LUMO gap is more reactive and is considered as soft [27]. According to HSAB concept, hard acids prefer binding to the hard bases to give ionic complexes, whereas the soft acids prefer binding to soft bases to give covalent complexes. This gap in m^5Cyt is 9.20 eV and for Cyt is 9.51 eV.

In the context of HSAB theory stated above makes m^5Cyt soft and therefore more reactive than Cyt in biological environments and susceptible to bond to reactive mutagenic species by forming covalent bonds.

Once m^5Cyt is ionized the cation may irreversibly deprotonate at C5-CH_3 producing the 3αH radical [43]. This irreversible deprotonation can halt hole transfer in DNA [39]. In this context the radiation-induced damage to DNA should not be studied only at the guanine N7 site alone but to consider also the ionization of m^5Cyt [44,45]. Finally, in an experimental investigation on the reactions of m^5Cyt cation radicals employing electron spin resonance (ESR) spectroscopy it was shown that the m^5Cyt is a "mutational hot spot" on photolysis by γ-radiolysis of double-stranded DNA oligomers [46]. In recent years m^5Cyt is considered as the fifth nucleobase of DNA and this is associated with the discovery that the methyl group of this epigenetic mark can undergo iterative enzymatic oxidation in self-renewing, pluripotent and neuronal cells as part of a likely demethylation pathway [47].

The cations of Cyt and m^5Cyt are highly unstable because they are susceptible to rapid deamination upon saturation of 5,6-double bond or deprotonation of N8. For deprotonated radicals and related anions derived from Cyt, the N-centered radical species lie lower in energy than the C-centered species. The energetic orders were reported in a theoretical (DFT) and experimental (ESR) investigation [48,49]. The two N8-centered radicals **7** and **8** have similar geometries; however, radical **8** lies energetically by 5 kcal/mol below radical **7** [48,49].



Therefore, in the iminyl σ-radical, the unpaired spin is localized on the exocyclic nitrogen in an in-plane pure *p*-orbital [49].

3.2. Activation barriers for cytosine methylation at the N3 site by methane diazonium ion

The methylation reaction mechanism of Cyt at the N3 site with methane diazonium ion is an S_N2 reaction characterized by the fact that the N3 Cyt site, the dinitrogen leaving group (N_2) and the carbon atom of methane diazonium ion are approximately linear. In a typical S_N2 reaction the attack angle must be at 180° because this angle provides the maximum overlap between the lone pair of electrons on the Cyt reaction center and the σ* antibonding orbital of C – X, (X = leaving group). The leaving group (dinitrogen) is then pushed off the opposite side and the product is formed.

Table 2 contains gas- and aqueous-phase transition state geometries and activation energies for the methylation of cytosine at the N3 site corrected for the zero-point-energy. It contains also the distances for forming and breaking bonds calculated at the DFT/M06-2X/6-311 + G** and the C-PCM reaction field level of theory. The activation energy of the gas-phase methylation reaction at the N3 site is 5.84 Kcal/mol and in water is 5.50 Kcal/mol. The imaginary frequency for the gas-phase reaction at the N3 site is 151 cm^{-1}. In water the imaginary frequency is 249 cm^{-1}. Table 2 lists also the breaking and forming bond distances in the transition state of the methylation reaction of Cyt at the N3 site at both in gas-phase and water.

Table 2
Gas-phase and in water transition-state geometries and activation energies of methylation of cytosine and its derivatives by methane diazoniumion using the DFT/M06-2X/6-311 + G** and C-PCM level of theory.

Molecule	Site	r_{form} (Å)	r_{break} (Å)	Attack Angle (deg)	E_a (Kcal/mol)
Gas phase					
Cyt	N3	2.365	1.581	174.68	5.837
Water					
Cyt	N3	2.290	1.601	177.24	5.502

Fig. 2 shows the transition state geometries of the methylation reaction of Cyt at the N3 in the gas-phase, structure (a), and in water, structures (b). The attack angle N3-C1-N5 is close to linearity in both gas-phase (174.68°) and in water (177.24°). Consequently, the activation energy is 5.502 Kcal/mol in water, lower by 0.33 Kcal/mol than that in the gas-phase. This finding can be attributed to the fact that the angle of attack becomes more linear in water than at the gas phase. In addition, the forming bond distance in water is 2.290 Å, and it is shorter by 0.075 Å than in the gas phase and the leaving distance is longer in water (1.601 Å) than in the gas phase (1.581 Å). This shows that the transition state in water is tighter than in the gas phase.

In small charged reactants, such as methane diazonium ion, charge is concentrated and in the transition states charge is more delocalized. This difference in charge localization gives rise to the activation barriers because it makes the stabilization due to solvation greater for the reactants than in the transition states.

We repeat the same calculations by employing the DFT/3LYP/6-31 + G*/SM8. We do this to compare the values of the activation energies and the results are listed in Table B in Supporting Information. In Table B, the gas-phase activation barrier is 7.22 kcal/mol and in water is 7.33 kcal/mol. In this calculation the gas-phase transition state geometry was retained in water using the SM8 Universal Solvation Model. Here the geometry of the molecule in water remains the same as in the gas-phase. In these calculations the activation energy in water is larger by 0.1 kcal/mol than in the gas phase. This result follows the trend that the activation energy increases because of hydration effects as reported in [14]. The activation energy barrier in water (5.50 kcal/mol) calculated by the DFT/ M06-2X/6-311 + G**/C-PCM level of theory is larger by 0.2 kcal/mol than the previously obtained one by using the B3LYP/6-31 + G* and C-PCM [14]. We believe that this difference in the values of activation barriers can be attributed to the dispersion-corrected density functional, M06-2X, and to the larger basis set we used herein for better energetics.

It is important to note that the interaction of water molecules with

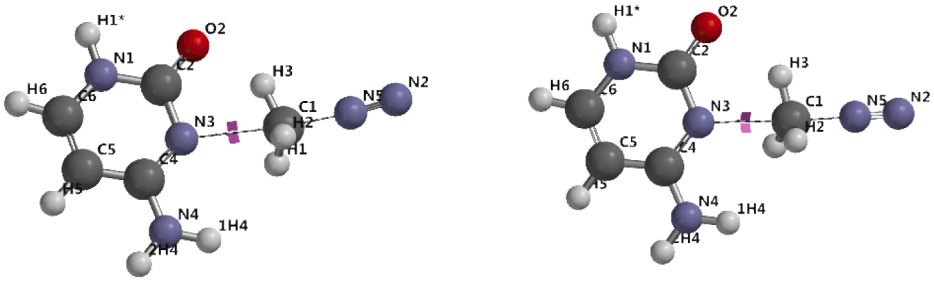


Fig. 2. Gas- and aqueous- phase transition state structures optimized at the DFT/M06-2X/6-311 + G** level of theory and the C-PCM model of Cyt at the N3 site. Table 2 lists the forming and breaking bond distances.

the reaction system is a dynamic process and the structures of the hydrated complex structures are not likely to persist but they have only a statistical significance in the determination of the energy of the activation barriers. This motivates us for future investigations to more accurate computation of solvated systems using explicit hundreds of water molecules in MD simulations, sampling all possible solvent arrangements in the evaluation of Gibbs energy of hydration.

4. Conclusions

The main conclusions of this investigation are:

)a. The fact that, as the first π ionization potential of the nucleotide base decreases, the base reactivity increases motivated us to evaluate the VIP_{aq} of Cyt and m^5Cyt in water. The VIP_{aq} values are approximately 5.11 eV for Cyt, and it decreases as Cyt is getting methylated (m^5Cyt) to approximately 4.86 eV. And the AIP_{aq} of Cyt is approximated to be 4.90 eV and it is decreased by 0.27 eV for m^5Cyt to approximately 4.63 eV.

)b. The significant decrease of the aqueous IPs of m^5Cyt alarms us that the radiation-induced damage to DNA should not be studied only at the guanine N7 site alone but to consider also the ionization of m^5Cyt

)c. In the context of the HSAB, the HOMO-LUMO gap for m^5Cyt is 9.20 eV and for Cyt is 9.51 eV and this makes m^5Cyt soft and therefore more reactive in the context of the hard and soft acids and bases theory. The soft acids and bases make covalent bonds as such exist in biological environments.

)d. The creation of a mutant by methylation of Cyt by the carcinogenic methane diazonium ion at the N3 site for both gas-phase and in water follows the S_N2 mechanism and in this investigation, the activation barrier at the gas-phase is approximately 5.84 eV and it lowers to 5.50 eV in water. The attack angle in water is close to linearity (177.24°) and the forming bond distance in the transition state in water is shorter than in the gas phase making it more tight.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cplett.2020.137544.

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